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SWOG 1918: A Phase II/III randomized study of R-miniCHOP with or without oral azacitidine (CC-486) in participants age 75 years or older with newly diagnosed aggressive non-Hodgkin lymphomas - Aiming to improve therapy, outcomes, and validate a prospective frailty tool

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Abstract

Diffuse large B cell lymphoma (DLBCL) is an aggressive but potentially curable malignancy; however, cure is highly dependent on the ability to deliver intensive, anthracycline-based chemoimmunotherapy. Nearly one third of cases of DLBCL occur in patients over age 75 years, and advanced age is an important adverse feature in prognostic models. Despite this incidence in older patients, there is no clear accepted standard of care due to under-representation of this group in large randomized clinical trials. Furthermore, insufficient assessments of baseline frailty and prediction of toxicity hamper clinical decision-making. Here, we present an ongoing randomized study of R-miniCHOP chemoimmunotherapy with or without oral azacitidine (CC-486, Onureg) for patients age 75 and older with newly diagnosed DLBCL and associated aggressive lymphomas. The incorporation of an oral hypomethylating agent is based on increased tumor methylation as a biologic feature of older patients with DLBCL and a desire to minimize the injection burden for this population. This is the first randomized study in this population conducted in North America by the National Clinical Trials Network (NCTN) and will enroll up to 422 patients including 40 patients in a safety run-in phase. This study incorporates an objective assessment of baseline frailty (the FIL Tool) and a serial comprehensive geriatric assessment (CGA). Key correlative tests will include circulating tumor DNA (ctDNA) assays at pre-specified timepoints to explore if ctDNA quantity and methylation patterns correlate with response. S1918 has the potential to impact future trial design and to change the standard of care for patients 75 years and older with aggressive lymphoma given its randomized design, prospective incorporation of geriatric assessments, and exploration of ctDNA correlatives.

Trial registration: The trial is registered with ClinicalTrial.gov Identifier NCT04799275

Keywords

DLBCL; lymphoma; geriatric; older; azacitidine; ctDNA

1. Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of Non-Hodgkin lymphoma (NHL), with 5.4 cases per 100,000 Americans in 2018 (1). It is an aggressive malignancy but potentially curable with anthracycline-based chemoimmunotherapy. According to SEER data, nearly one third of cases of DLBCL will be diagnosed in patients aged 75 and older (1). Despite the increased frequency in older patients and inferior outcomes, patients in this age group typically account for < 10% of patients enrolled in National Cancer Institute (NCI) cooperative group trials (2). There is currently no standard of care for older patients, who frequently are frail and with comorbidities, and physicians must extrapolate treatment decisions from trials conducted in younger and healthier patients. Studies for the older population have been largely single-arm and highly variable in their eligibility criteria (Table 1). R-miniCHOP, a dose attenuated version of standard R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), is often chosen based on a prospective, single-arm phase II trial which showed a 2-year progression-free survival (PFS) of only 47% (3), with obvious and significant room for improvement.

A key dilemma for the practicing physician is identifying which older DLBCL patients may be considered for curative intent chemoimmunotherapy, and which should be treated with a palliative approach; the challenge is to avoid both over-treatment with excessive toxicity

and under-treatment with inferior outcomes (4). The FIL (Fondazione Italiana Linfomi; Italian Lymphoma Foundation) has developed a frailty assessment tool accounting for age, comorbidities, and ability to perform activities of daily living (ADLs) and instrumental activities of living (IADL). The FIL Tool classifies patients as "fit," "unfit," or "frail" (5). When the FIL tool was prospectively applied to 1163 patients, 55% were fit, 28% were unfit, and 18% were frail. Three-year OS for the whole cohort was 65% and was strongly driven by fitness: 3-year OS was 75% for fit patients, 58% for unfit, and 43% for frail; similar outcomes were seen in a validation cohort (6). While this analysis showed the prognostic value of frailty assessment, treatment varied and was at the discretion of the treating physician.

Epigenetic deregulation is a feature of DLBCL in older patients and provides a rationale for targeting methylation. Pre-clinical models show that pre-treatment with hypomethylating agents improves the anti-tumor effect of the agents contained in R-CHOP (7). This work has led to early clinical studies of the hypomethylating agent azacitidine with R-CHOP in newly diagnosed DLBCL, with promising early efficacy and acceptable toxicity. Azacitidine has been used in older patients for other disease states (namely acute myeloid leukemia [AML] and myelodysplastic syndrome [MDS]), and is both active and well-tolerated. Oral azacitidine (CC-486 or Onureg) is FDA-approved for maintenance therapy for patients with AML who achieve a compete response (CR) or CR with incomplete count recovery (CRi) but are unable to receive additional intensive chemotherapy. The availability of an oral agent targeting aberrant methylation is an appealing additive approach.

Based upon the need for improved outcomes in older patients, and the rationale and promise of azacitidine in this setting, the National Clinical Trials Network (NCTN), led by SWOG, developed S1918, a randomized trial comparing R-miniCHOP to R-miniCHOP with oral azacitidine for older patients (age 75) with newly diagnosed aggressive B-cell non-Hodgkin lymphomas (NHLs). This study incorporates the FIL tool for frailty assessment and a serial comprehensive geriatric assessment (CGA) to evaluate effects of therapy on functional status over time.

2. Methods and Design

2.1 Study design and main objectives

S1918 is a randomized, open-label phase II/III study with safety run-in enrolling patients age 75 and older with newly diagnosed DLBCL and related aggressive NHLs, including those transformed from low-grade lymphoma (except Richter's transformation from CLL) and double-hit lymphomas (Figure 1). Enrolled patients will be randomized to receive R-miniCHOP chemotherapy (rituximab IV 375mg/m2, cyclophosphamide IV 400mg/m2, doxorubicin IV 25mg/m2, vincristine IV 1mg on day 1; oral prednisone 40mg/m2 on days 1-5) with or without oral azacitidine (200mg orally on days 1-7 of priming for cycle 1, days 8-21 of cycles 1-5). Of note, subcutaneous rituximab with hyaluronidase human (1400mg) can be used for cycles 2-6. There will be 3 stratification factors for randomization: 1) age 75-79 years vs. 80 years and above, 2) transformed lymphoma vs. *de novo*, and 3) international prognostic index (IPI) score of 1-2 vs. 3 or greater. This is a NCTN study run

by SWOG and developed in collaboration with Alliance and ECOG-ACRIN. This study is available at any center in the US with access to NCTN trials.

Up to the first 44 (40 evaluable) patients enrolled are part of a randomized safety run-in (Figure 2). The primary objective of this run-in is to determine if the addition of 200mg oral azacitidine to R-miniCHOP results in excess toxicity compared to R-miniCHOP alone. Given that deaths can be seen with R-miniCHOP alone in this patient population (3), a randomized run-in phase was chosen to more precisely assess toxicity. During this safety run-in, patients will be evaluated weekly with lab tests and either an office visit or telemedicine follow up during cycle 1 (C1). The study team and treating investigators will have bi-weekly safety calls during this run-in period. There will be a pause in enrollment after the first 40 evaluable patients have completed cycle 1 of therapy. If there are four or fewer grade 5 events in each arm and no other concerning safety signals emerge, these 40 patients will be included as part of the randomized phase II/III component.

The primary objective of the phase II component will be to determine if there is sufficient evidence to continue enrollment to complete the phase III trial by evaluating whether there is improvement in the 1 year PFS in the oral azacitidine + R-miniCHOP arm compared to the control of R-miniCHOP alone. The primary objective of the phase III component is to compare the OS between oral azacitidine + R-miniCHOP and R-miniCHOP alone.

This study has been approved by the National Cancer Institute Adult CIRB.

2.2 Patient population

Patients eligible for S1918 are age 75 and older with newly diagnosed DLBCL and related aggressive lymphomas which are stage II bulky, stage III, or stage IV by Ann Arbor staging. Patients with grade 3b follicular lymphoma (FL) are also eligible, as these patients are typically treated as having DLBCL. Patients with lymphomas that have translocations in *cMYC* and *BCL2* and/or *BCL6* are eligible. As noted, patients with transformed lymphomas (except for Richter's transformation from CLL) are also eligible. Prior therapy for low-grade lymphoma is allowed. Eligible patients have a Zubrod performance status of 2 or less, a creatinine clearance of 30 mL/minute or greater, and an ejection fraction (EF) of 45% or better. Patients with hepatitis C, hepatitis B, and/or human immunodeficiency virus (HIV) are eligible if these infectious diseases are controlled with negative viral loads. Eligibility were chosen to be responsive to the American Society for Clinical Oncology (ASCO) and Friends of Cancer recommendations for increasing access to clinical trials. Key exclusion criteria include grade 2 or higher neuropathy. Patients must have an absolute neutrophil count (ANC) of 1000 or better and platelets of 75,000 or better unless cytopenias are due to lymphomatous involvement of the bone marrow. Patients with any known central nervous system (CNS) involvement by lymphoma are excluded.

2.3 Treatment Plan

2.3.1 Prephase therapy—Prephase therapy has been shown to improve performance status and decrease early treatment-related mortality (8, 9). All patients will receive prephase therapy with prednisone prior to starting treatment on their assigned arm. Prednisone pre-

phase may begin prior to formal study enrollment and should be completed no more than 14 days prior to starting oral azacitidine priming (arm 1) or R-miniCHOP (arm 2). Dose and duration of prednisone are at the discretion of the treating investigator within the following parameters: 60-100mg of prednisone daily for 4-7 days.

2.3.2 Treatment arms

2.3.2a   Arm 1: oral azacitidine + R-miniCHOP (Table 2): Patients randomized to this arm will receive 7 days of oral azacitidine "priming" prior to cycle 1 day 1 of R-miniCHOP. R-miniCHOP will then be administered on day 1 every 21 days for 6 cycles. For cycles 1-5, patients will take oral azacitidine (200mg) on days 8-21 as priming for the next dose of R-miniCHOP. All patients are expected to receive filgrastim, pegfilgrastim, or any biosimilar growth factor as prophylaxis for febrile neutropenia.

2.3.2b   Arm 2: R-miniCHOP (Table 3): Patients randomized to this arm will receive R-miniCHOP as noted above on day 1 of a 21-day cycle for 6 cycles. Growth factor prophylaxis will be required for this arm as well.

2.4 Follow up

After completion of study therapy, follow up visits are planned every 3 months for the first year, then every 6 months or the second year, and then annually until 5 years from the date of registration or until time of progression or death.

This study follows the NCI Adverse Event Reporting Guidelines and utilizes the Rave® / Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). Serious adverse events (SAEs) must be reported within 24 hours.

2.5 Correlative assessments

2.5.1   Geriatric assessments—Based on the data from the FIL group, we hypothesize that patients who scored as fit or unfit via the FIL tool will have an improved OS compared to those who score as frailwhen treated with R-miniCHOP +/– oral azacitidine. The FIL tool will be administered at the time of study enrollment. If our hypothesis is correct, the FIL tool could be used in the future to select candidates for chemoimmunotherapy with curative intent.

We also intend to use this study as an opportunity to learn about effect of chemoimmunotherapy on patient functioning in both the short and long term. Longitudinal geriatric assessments have not been incorporated into studies in this population to date. We will utilize the CGA that has been developed and implemented in the intergroup setting by the Alliance Cancer and Aging Research Group (CARG) (10). The S1918 CGA will be performed at 4 timepoints (baseline, 6 months after registration, 12 months after registration, and 24 months after registration) in order to capture both immediate and long-term effects of therapy.

2.5.2   Laboratory Correlatives—Specimens will be collected for circulating tumor DNA (ctDNA) assays. 40 mL of peripheral whole blood are to be collected in three 10-ml

Streck Cell-Free DNA BCT tubes and two 5-ml Streck Cyto-Chex tube at the following timepoints:

- Arm 1: (1) prior to CC-486 priming, prior to R-miniCHOP on (2) Cycle 1/Day 1 and (3) Cycle 2/Day 1, (4) 12 months after registration, (5) 24 months after registration, (6) at time of progression

- Arm 2: prior to R-miniCHOP on (1) Cycle 1/Day 1 and (2) Cycle 2/Day 1, (3) 12 months after registration, (4) 24 months after registration, (5) at time of progression

2.6 Statistics

The primary endpoint of the phase II component of the study is PFS. Based on previous data, we assume the 1-year PFS for the control arm (R-miniCHOP alone) will be 50%. After accruing 130 participants (65 per arm, 21 months of accrual and potentially pausing accrual for 6 months follow-up to reach a target 63 events across arms), a one-sided stratified .10 log-rank test will inform a go/no-go decision based on sufficient evidence of efficacy to continue to the Phase III portion of the study. The power of this test with an alternative of hazard ratio 1.86 (corresponding to 1-year PFS of 69% for the experimental arm versus 50% for the control arm) is 88%.

The primary endpoint of the phase III component is OS. Based on an expected 2-year OS of 59% for this population treated with R-miniCHOP, with 384 eligible participants randomized over 5 years and 2 additional years of follow-up, a 1-sided .025 level stratified logrank test will have 90% power to detect a hazard ratio of 1.55 (corresponds to an improved 2-year overall survival from 59% in the control arm to 71% in the experimental arm).

3. Discussion

S1918 is one of the first randomized trials in the modern therapeutic era focusing on older patients with DLBCL in North America. According to US Census estimates, people age 65 and older were estimated to be 17.5% of the population in 2019 (11), and this proportion continues to increase. Older patients also constitute the majority of patients with DLBCL. Despite data that overall survival is higher in older patients receiving rituximab-containing regimens, a 2014 assessment of Medicare-SEER data found that 23% of patients age 66 years and older and 33% of patients 80 years or older do not receive any therapy at all for this potentially curable disease (12). For patients 66 years and older, probability of survival at 60 months was approximately 10% for untreated individuals versus approximately 40% for those who received just rituximab and 65% for those who receiving rituximab with chemotherapy (12). The improved outcome with treatment is countered by a 29% risk of congestive heart failure with doxorubicin use in patients 65 years and older, particularly in patients with pre-existing cardiovascular risk factors (hypertension, prior cardiovascular disease, etc) (13). Thus, while there appears to be a survival benefit when older patients with DLBCL are treated with chemoimmunotherapy, there is also a clear need for baseline toxicity prediction and targeted regimens that attenuate the chemotherapy component.

R-miniCHOP (3) has been adopted widely for the treatment of older patients with DLBCL or those with multiple co-morbidities. In a registry study that retrospectively assessed 73 patients receiving R-miniCHOP, 1-year PFS was 51% and 1-year overall survival (OS) was 60% (14). For comparison, patients age 18-60 treated with R-CHOP-like therapy have a 2 year OS of about 95% (15), and those age 60-80 have a 2-year OS of approximately 75% with R-CHOP chemotherapy (16). R-miniCHOP was the control arm for the SENIOR study from the French LYSA group. SENIOR was a randomized phase III study of patients age 80 and older with newly diagnosed DLBCL randomized to R-miniCHOP or R-miniCHOP with the immune modulatory drug lenalidomide 10mg daily on days 1-14 of each cycle (R2-miniCHOP). The study did not reach its primary endpoint of improving 2-year OS with the addition of lenalidomide. 2-year OS was 66% in the R-miniCHOP arm and 65.7% in the R2-miniCHOP arm. Grade 3+ toxicities were greater in the R2-miniCHOP arm (81% vs 53%)(17). The reasons for this being a negative trial are complex (4). Thus, R-miniCHOP remains the standard chemoimmunotherapy regimen for older DLBCL patients.

The hypomethylating agent azacitidine is a rational addition to R-miniCHOP based on several considerations. First, there is evidence that methylation of tumor-suppressor genes increases with age (18), and aberrant DNA hypermethylation of tumor-suppressor genes is reported in DLBCL (19). There is significantly more methylation of CpG islands and CpG shores in DLBCL tumor samples compared to normal, non-neoplastic tissue. In patients who subsequently relapse, there is increased intratumoral heterogeneity in methylation at diagnosis compared to tumor samples from those who do not relapse (19). Thus, increased epigenomic deregulation appears to be an important mechanism for tumorigenesis and therapy resistance in DLBCL. In a phase I study of subcutaneous azacitidine followed by standard R-CHOP chemotherapy in patients (median age 65 year) with newly diagnosed DLBCL, 10/12 patients remained in a complete remission at 13 months of follow up. *Ex vivo* analysis of tumor specimens showed that tumor cells were more responsive to chemoimmunotherapy after exposure to azacitidine (7).

The oral formulation of azacitidine was subsequently studied in combination with standard R-CHOP in 59 patients with a median age of 66 years. The recommended phase II dose for oral azacitidine in combination with full-dose R-CHOP was 300mg. Overall, the treatment was well-tolerated. Response rates were excellent with an overall response rate (ORR) of 95% and a CR rate of 88%. Estimated 1 year and 2 year PFS at the time of last study presentation were 86% and 78% (20). S1918 represents an opportunity to extend these promising results to the older patient population. However, febrile neutropenia was more common in the patients older than 70 years, and subsequent pharmacokinetic analyses suggest similar parameters for 200mg compared to 300mg. Given these factors, we have chosen 200mg oral azacitidine as the dose to use in S1918.

An essential need in older populations is to assess baseline status, predict toxicity, and understand the impact of treatment on function. Single arm and retrospective analyses emphasize the importance and impact of objective frailty measures and correlations with improved outcomes in DLBCL. S1918 will utilize the FIL tool which was specifically designed to assess baseline functionality in older patients with newly diagnosed DLBCL. This tool identifies 3 risk groups: fit, unfit, and frail (5, 6). In a prospective study of

patients who were categorized as fit using the FIL tool and treated with combination chemoimmunotherapy, overall survival at 5 years was about 60% (21). In contrast, patients who scored as frail using the FIL tool were treated with a variety of regimens at the treating investigator's discretion and found to have a 5-year OS of 33%. Interestingly, this 5-year OS for frail patients was similar whether or not the patient received rituximab (22).

The FIL tool has also been applied retrospectively to a cohort of 205 patients age 65 and older in Australia (median age 73). In this cohort, 41% were classed as fit, 21% as unfit, and 38% as frail. Patient who were identified as frail had inferior OS compared to the fit patients (HR 2.89). There was not a significant difference in OS between those who were fit and unfit; OS at 5 years was 60% for fit patients, about 55% for unfit, and about 25% for frail. 65% of patents classified at frail received R-CHOP, and these patients had high rates of unplanned admissions (63%), early treatment cessation (75%), and treatment-related death (80%) compared to the fit and unfit patients (23). Thus, available data to date suggests that fit and unfit patients via the FIL tool are likely to benefit from combination chemoimmunotherapy, while those scoring as frail are perhaps best treated with a palliative approach. We hypothesize that this will be the finding in S1918 as well. We also hypothesize that those who are found to be fit or unfit will have an improved OS compared to those who score as frail, and that the FIL tool may be used in the future to select patients best suited for chemoimmunotherapy with curative intent. The FIL Tool has not yet been fully validated for selecting therapy for an individual patient, and S1918 could strengthen the evidence in favor of using it as an integrated tool.

The FIL Tool will be applied once at study enrollment. In contrast, the S1918 CGA will be applied at multiple timepoints. We will be comparing if there is a difference in functioning via this CGA between the 2 arms. The CGA has both patient and provider components examining multiple dimensions of physical and cognitive functioning, including functional status, comorbidities, cognitive function, psychological state, social supports, and nutritional status. When this CGA was implemented in a cooperative group setting, patients (ages 65-90, median age 72) took a median of 15 minutes to complete their portion of the CGA. 87% of patients were able to complete their portion without assistance. Healthcare professionals took a median of 5 minutes to complete their portion; median total time to complete both the patient and healthcare was 22 minutes, demonstrating feasibility of administering this CGA in the setting of a cooperative group trial (10). Although it is currently under investigation in other trials, it has not been used in a lymphoma trial to date. S1918 will also be the first trial to use this CGA in serial assessments, making this longitudinal assessment of functioning in this population a unique feature of this study.

There is emerging evidence that circulating tumor DNA (ctDNA) can predict responses to therapy in DLBCL. In retrospective assays, a 2-log reduction in ctDNA after 2 cycles of therapy is associated with improved event-free survival (83% vs 50%) (24). S1918 will collect ctDNA prior to enrollment, prior to cycle 1 day 1 (C1D1), prior to C2D1, 12 months after registration, and 24 months after registration. In addition to the quantity of ctDNA, methylation patterns both in the ctDNA itself and in normal T cells will be evaluated. These are exploratory analyses aimed at better understanding the effects of hypomethylating agents on both tumor DNA and normal cells in this population. The impact of treatment on ctDNA

quantity or methylation status may help drive the design of future studies as it relates to the incorporation of hypomethylating strategies.

S1918 has the potential to establish a new standard of care as well as a more precise means of evaluating older patients with DLBCL. The prospective study of frailty assessment and toxicity prediction is badly needed at the bedside for practicing physicians, and there is an expectation that S1918 will address these challenges. There is carefully incorporated specimen banking, correlative assays based on the mechanism of action of azacytidine, and serial geriatric assessments. This national collaborative effort will yield the largest prospective dataset as part of a clinical trial to understand biology and optimal treatment of DLBCL in patients age 75 and older, and the first time this group has been studied by the NCTN in the modern therapeutic era. S1918 has the potential to change the therapeutic standard of care in its population but also to fundamentally change the approach to and selection fo therapy for older patients with newly diagnosed aggressive lymphomas.

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Figure 1:
Overall Study Schema

40pt safety lead-in
(1:1 randomization) → **STOP** after all have
completed C1

↓

Randomized Ph II
- 1° endpoint: 1 year PFS   130 eligible participants

↓

Randomized Ph III
- 1° endpoint: **2 year OS**   Total anticipated accrual =
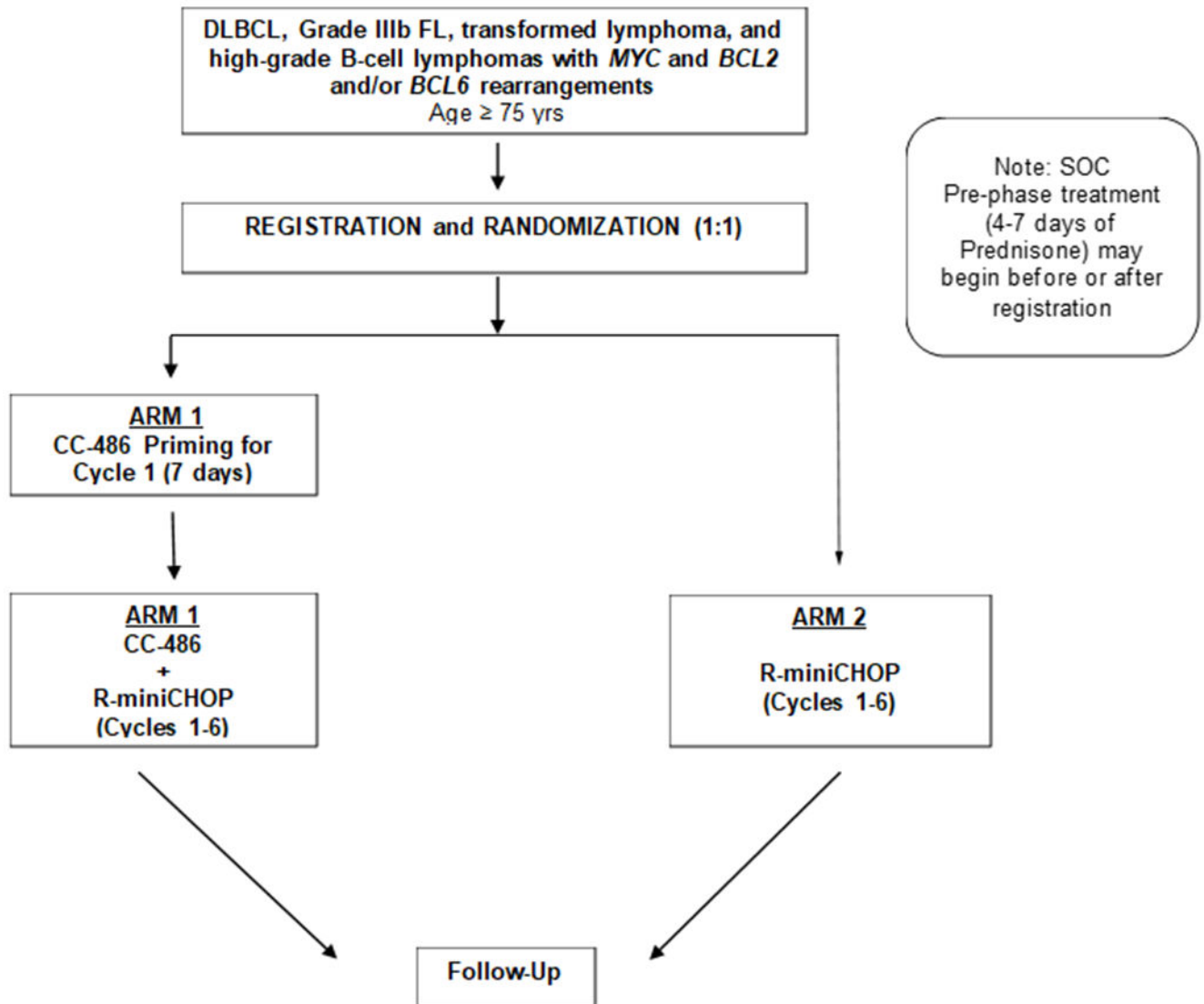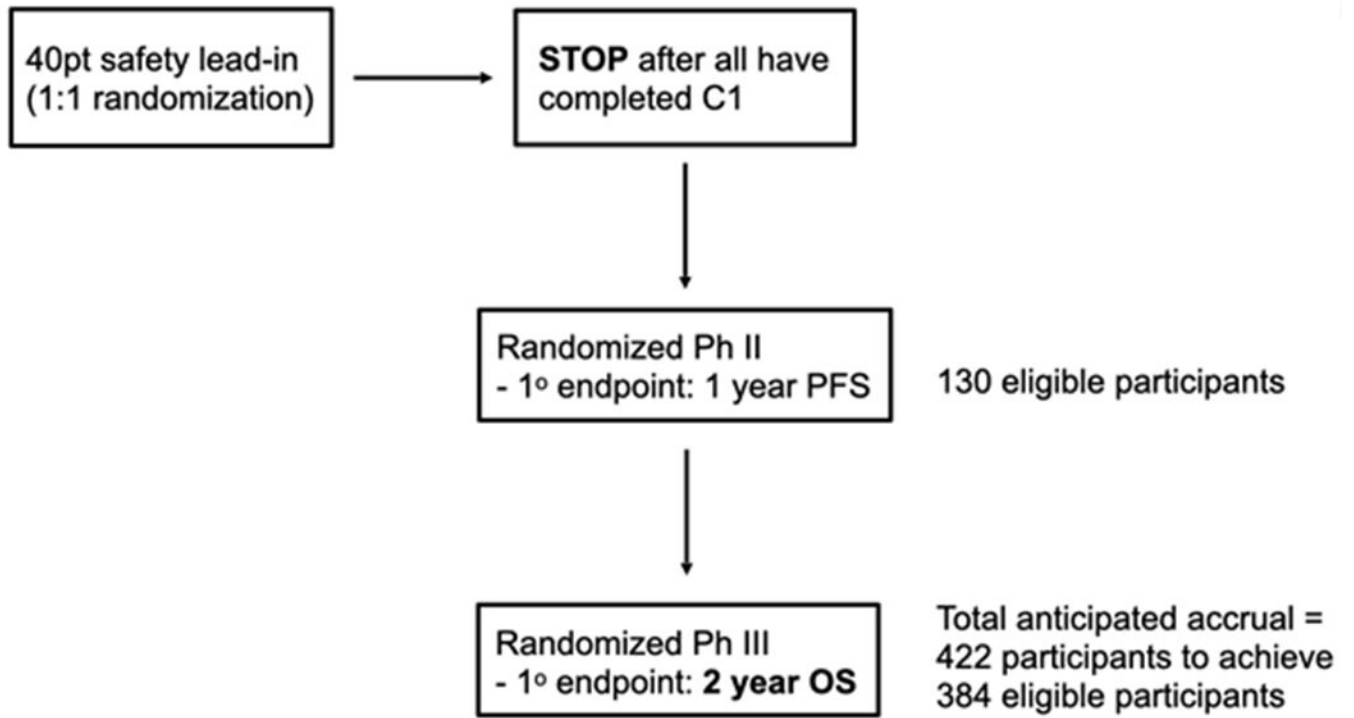422 participants to achieve
384 eligible participants

Figure 2:
Phase II/III design with safety lead-in

Table 1:

Prospective studies in newly diagnosed DLBCL focused on older patients and/or those with co-morbidities

Regimen (reference)	Key Inclusion Criteria	Median Age (years)	Arms	2 year OS	Pre-phase?	Geriatric Assessment?
R-miniCHOP (3)	80 years	83	R-miniCHOP	59%	No	None
R-70%CHOP (25)	70 years	76	R-70%CHOP	~65%	No	None
SENIOR Study (17)	80 years	83	1) R-miniCHOP 2) R-miniCHOP with lenalidomide 10mg	66% 65.7%	Yes	None
Ofatumumab-miniCHOP (26)	80 years	83	1000mg ofatumumab + miniCHOP	64.7%	Yes	None
Obinatuzumab-miniCHOP (27)	Age > 65, unfit via FIL tool	82	100mg obinutuzumab + miniCHOP	49%	No	FIL tool for entry
R-CGVP (28)	LVEF 50% or EF > 50% with cardiac co-morbidities	76	rituximab, cyclophosphamide, gemcitabine, vincristine and prednisone	55.8%	No	None
R-miniCEOP (21)	"Fit," age > 65 years	72	R-CHOP R-miniCEOP - rituximab, cyclophosphamide, epirubicin, vinblastine, prednisone	~65% ~70%	No	ADLs and CIRS-G. "Fit" was defined at ADL score of or better, fewer than grade 3 CIRS-G co-morbidities and no grade 4 co-morbidities.
Mosuntuzumab (29, 30)	80 years OR 60-79 years and impairment in 1 or more ADL or IADL or impairment of renal, cardiac, or haptic function precluding use of chemoimmunotherapy	84	CD20-CD3 bi-specific antibody	Not yet reported; ORR 67.7% (41.9% CR)	No	ADL or IADL assessment for inclusion for those < 80

Table 2:

Treatment plan - Arm 1

2a. Priming for Cycle 1

			Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Azacitidine	200mg	Oral	x	x	x	x	x	x	x

2b. Cycles 1-5

			Day 1	Day 2	Day 3	Day 4	Day 5	Day 8-21
Rituximab [*]	375mg/m2	IV	x					
Cyclophosphamide	400mg/m2	IV	x					
Doxorubicin	25mg/m2	IV	x					
Vincristine	1mg	IV	x					
Prednisone	40mg/m2	Oral	x	x	x	x	x	
Azacitidine	200mg	Oral						x

2c. Cycle 6 (no azacitidine)

			Day 1	Day 2	Day 3	Day 4	Day 5
Rituximab [*]	375mg/m2	IV	x				
Cyclophosphamide	400mg/m2	IV	x				
Doxorubicin	25mg/m2	IV	x				
Vincristine	1mg	IV	x				
Prednisone	40mg/m2	Oral	x	x	x	x	x

[*] subcutaneous rituxumab injection with hyaluronidase may be utilized for cycles 2-5

[**] any rituximab biosimilar may be used

Table 3:

Treatment Plan - Arm 2, Cycles 1-6

			Day 1	Day 2	Day 3	Day 4	Day 5
Rituximab [*]	375mg/m2	IV	x				
Cyclophosphamide	400mg/m2	IV	x				
Doxorubicin	25mg/m2	IV	x				
Vincristine	1mg	IV	x				
Prednisone	40mg/m2	Oral	x	x	x	x	x

[*]
subcutaneous rituxumab injection with hyaluronidase may be utilized for cycles 2-5

[**]
any rituximab biosimilar may be used